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Editorial

Clinical Research in Pulmonary Hypertension Comes of Age☆

La investigación clínica en hipertensión pulmonar ha alcanzado la mayoría de edad

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The first randomized clinical trial with epoprostenol in patients with pulmonary arterial hypertension (PAH) was published 18 years ago.[1] This trial was the first in a series of controlled clinical trials which subsequently defined the current therapeutic approach to this devastating disease.[2] That these outstanding advances could be achieved in such a short period of time is the result of basic researchers and clinicians, pharmaceutical companies and regulatory agencies joining forces in the rapid "translation" of laboratory concepts into clinical practice.

Data are now available from over 30 controlled clinical trials and several meta-analyses, from which evidence-based therapeutic algorithms in PAH have been developed.[2] In most of these trials, the change in distance covered in the 6-minute walking test (6MWT) was used as the primary endpoint. This variable provides information on the patient's symptoms and ability to perform daily activities, and is a predictor of mortality.[3] The 6MWT is a simple, low-cost, reproducible test that is widely available.

However, 6MWT also has its limitations. Firstly, the change in distance walked is influenced by the baseline value and presence of comorbidities, and a "ceiling" effect has been observed,[4] that is to say, the distance achieved in the initial months does not increase even if treatment is continued. Secondly, the test is not particularly sensitive to the effect of starting a new drug in patients already under treatment. Thirdly and more importantly, there is no correlation between changes in the 6MWT seen in the early months and long-term mortality.[5]

This critical analysis of the 6MWT as a primary endpoint in PAH clinical trials led to the proposal raised in the Fourth World Symposium on Pulmonary Hypertension (Dana-Point, 2008) of using composite endpoints associated with long-term morbidity and mortality in clinical trials.[6] Specifically, the use of time to clinical worsening was suggested as a primary endpoint. This is a composite endpoint that includes all-cause mortality, unscheduled hospitalization due to PAH, and clinical progression.[6]

The Dana-Point proposal has been taken up in the designing of several clinical trials, the first of which was the recently published *Study with an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcomes* (SERAPHIN).[7] The aim of this study was to investigate whether long-term treatment with macitentan, a new dual endothelin receptor antagonist, reduced morbidity and mortality in PAH patients. A total of 742 patients were included in the study, which evaluated 2 doses of macitentan *versus* placebo. The primary endpoint was time from start of treatment to the first PAH-related clinical event or all-cause mortality. PAH-related events were transplantation, atrial septostomy, initiation of intravenous prostanoids or clinical worsening–worsening of 6MWT or symptoms or need for a new treatment. Mean study duration was 85–104 weeks, depending on the groups. The study showed that, compared to placebo, macitentan reduced the risk of a PAH-related event.[7] In most cases the first event was worsening of PAH. In previously untreated patients, a significant treatment effect was observed with the 2 study doses, while in patients who were already receiving treatment the effect was only significant for the higher dose. The effect of macitentan on death or PAH-related hospitalization was also analyzed as a secondary endpoint. The risk diminished significantly with both dose levels. However, the main component of this endpoint was PAH-related hospitalization, while the effect on death as a first event was not significant.[7] This finding stems from the fact that death is not usually the first event to occur; it is more common that hospitalization due to clinical worsening precedes death.

The SERAPHIN trial is the first of a new generation of PAH trials featuring a more robust design and endpoints of clinical interest. Other trials studying morbidity and mortality as primary endpoints are currently underway. Of particular importance is the *Study of First-Line Ambrisentan and Tadalafil Combination Therapy in Subjects with Pulmonary Arterial Hypertension* (AMBITION), evaluating the strategy of initiating treatment with a combination of 2 drugs compared to conventional monotherapy.

The results of clinical trials with new drugs have recently been published. Hoeper et al.[8] were the first to evaluate the effect of imatinib, an antiproliferative tyrosine kinase inhibitor, in PAH. This agent has previously been used in the treatment of chronic myeloid leukemia. The findings show that while imatinib improved exercise capacity and pulmonary hemodynamics in patients with advanced PAH already receiving combined treatment, the active treatment group developed significant adverse events, primarily subdural hematoma. For this reason, application for approval of imatinib in PAH has been withdrawn. Ghofrani et al.[9,10] evaluated the effect of the soluble guanylate cyclase stimulator (sGC) riociguat on the distance walked in the 6MWT in patients with PAH[9] and chronic thromboembolic pulmonary hypertension (CTEPH).[10] SGCs are a new generation of compounds that act on the nitric

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oxide signaling pathway, increasing intracellular levels of cyclic guanosine monophosphate, producing a vasodilatory effect. Riociguat increased exercise capacity in both HAP and CTEPH patients. For this reason, riociguat was the first drug to receive approval in Europe for the indication of inoperable CTEPH or persistent CTEPH after pulmonary endarterectomy. Time to clinical worsening was also evaluated in these studies, but as a secondary endpoint, riociguat was shown to be beneficial in PAH patients.

Clinical research in pulmonary hypertension has made good progress, and 18 years after the publication of the first controlled clinical trial it is safe to say that it has finally come of age. Modern clinical trial designs are clearly oriented toward evaluating morbidity and mortality in a large patient population, follow-up periods are extensive, and new therapeutic routes, indications and treatment strategies are under investigation. This new generation of trials is providing data of great clinical importance, and there is little doubt that they will influence our approach to this disease in the near future.

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